C-reactive protein is not associated with the presence or extent of calcified subclinical atherosclerosis

Marc E. Hunt, MD, Patrick G. O’Malley, MD, MPH, Marina N. Vernalis, DO, Irwin M. Feuerstein, MD, and Allen J. Taylor, MD Washington, DC, and Bethesda, Md

Background Both high-sensitivity C-reactive protein (hsCRP) and electron beam computed tomography (EBCT) coronary artery calcification (CAC) are valid markers of cardiovascular risk. It is unknown whether hsCRP is a marker of atherosclerotic burden or whether it reflects a process (eg, inflammatory fibrous cap degradation) leading to acute coronary events.

Methods A nested case-control study was performed of 188 men enrolled in the Prospective Army Coronary Calcium study. The serum hsCRP levels (latex agglutination assay) were evaluated in subjects with CAC (CAC score >0, n = 94) and compared with age- and smoking status–matched control subjects (CAC score 0, n = 94).

Results Levels of hsCRP in the highest quartile were related to the following coronary risk factors: smoking status, low-density lipoprotein cholesterol, body mass index, glycosylated hemoglobin, fibrinogen, and homocysteine. The mean hsCRP level was similar in cases (+CAC, 0.20 ± 0.22 mg/dL) and controls (−CAC, 0.19 ± 0.21 mg/dL; P = .81) and was unrelated to the log-transformed CAC score (r < 0.01, P = .91). Multivariable analysis controlling for standard risk factors, aspirin, and statin therapy found only that low-density lipoprotein cholesterol was related to CAC.

Conclusions Despite associations with standard and emerging cardiovascular risk factors, hsCRP is unrelated to the presence and extent of calcified subclinical atherosclerosis. This implies that CAC (a disease marker) and hsCRP (a process marker) may be complementary for the prediction of cardiovascular risk. (Am Heart J 2001;141:206-10.)
Table I. Risk factor comparisons for coronary artery calcification and hsCRP subgroups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case (n = 93)</th>
<th>Control (n = 94)</th>
<th>Statistical significance</th>
<th>Case Control Statistical Highest Quartile</th>
<th>Quartiles 1-3 Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP (mg/dL)</td>
<td>0.20 ± 0.22</td>
<td>0.19 ± 0.21</td>
<td>P = .81</td>
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<tr>
<td>Body mass index (kg/cm²)</td>
<td>28.4 ± 3.1</td>
<td>27.7 ± 3.1</td>
<td>P = .14</td>
<td>29.5 ± 3.5 vs 27.6 ± 2.8 P = .001</td>
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<tr>
<td>Total cholesterol (mg/dL)</td>
<td>217 ± 38</td>
<td>202 ± 32</td>
<td>P = .003</td>
<td>220 ± 40 vs 206 ± 34 P = .02</td>
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<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>145 ± 35</td>
<td>134 ± 31</td>
<td>P = .03</td>
<td>147 ± 37 vs 137 ± 32 P = .05</td>
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<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>48 ± 12</td>
<td>49 ± 12</td>
<td>P = .75</td>
<td>48 ± 14 vs 49 ± 11 P = .59</td>
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<tr>
<td>Triglycerides (mg/dL)</td>
<td>145 ± 99</td>
<td>122 ± 63</td>
<td>P = .06</td>
<td>141 ± 79 vs 130 ± 85 P = .43</td>
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<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>124 ± 11</td>
<td>124 ± 12</td>
<td>P = .91</td>
<td>125 ± 12 vs 124 ± 11 P = .60</td>
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<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>77 ± 8</td>
<td>79 ± 14</td>
<td>P = .26</td>
<td>79 ± 9 vs 77 ± 12 P = .41</td>
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<tr>
<td>Hypertension (%)</td>
<td>27.0</td>
<td>22.0</td>
<td>P = .25</td>
<td>27.0 vs 22.0 P = .25</td>
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<tr>
<td>Current tobacco use (%)</td>
<td>8</td>
<td>8</td>
<td>NA</td>
<td>1.67 vs 4.3 P = .01</td>
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<tr>
<td>Glycosylated hemoglobin (%)</td>
<td>5.6 ± 0.5</td>
<td>5.6 ± 0.6</td>
<td>P = .60</td>
<td>5.7 ± 0.6 vs 5.5 ± 0.5 P = .04</td>
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<tr>
<td>Serum insulin (µU/mL)</td>
<td>8.4 ± 5.4</td>
<td>8.5 ± 8.7</td>
<td>P = .92</td>
<td>11.5 ± 11.8 vs 7.5 ± 4.6 P = .07</td>
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<tr>
<td>5-Year Framingham risk index (%)</td>
<td>2.1 ± 1.8</td>
<td>2.1 ± 1.5</td>
<td>P = .99</td>
<td>2.4 ± 1.4 vs 2.1 ± 1.7 P = .23</td>
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<td>Homocysteine (µmol/L)</td>
<td>9.9 ± 2.7</td>
<td>10.3 ± 2.3</td>
<td>P = .29</td>
<td>11.2 ± 3.1 vs 9.7 ± 2.2 P = .001</td>
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<td>Fibrinogen (mg/dL)</td>
<td>310 ± 59</td>
<td>301 ± 47</td>
<td>P = .23</td>
<td>342 ± 62 vs 293 ± 44 P &lt; .001</td>
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<tr>
<td>Lipoprotein(a) (mg/dL)</td>
<td>41 ± 41</td>
<td>30 ± 41</td>
<td>P = .07</td>
<td>32.8 ± 38.9 vs 36.4 ± 42.1 P = .61</td>
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LDL, low-density lipoprotein; HDL, high-density lipoprotein; NA, not available.

Results
The hsCRP level varied according to smoking status. Current smokers, ex-smokers, and subjects who denied a smoking history demonstrated levels of 0.34 ± 0.29 mg/dL, 0.21 ± 0.25 mg/dL, and 0.17 ± 0.19 mg/dL, respectively (P = .02). Table I displays the demographic and serologic measurements. Cases had significantly higher values for total and low-density lipoprotein (LDL) cholesterol as previously reported (Taylor et al, unpublished data).

The mean hsCRP levels were similar in cases and controls (0.20 ± 0.22 mg/dL vs 0.19 ± 0.21 mg/dL, P = .81, Figure 1). There was no relationship between the extent of CAC and the hsCRP level with use of log-transformed CAC values (r < .01, P = .91) (Figure 2). Subjects with hsCRP levels in the upper quartile had significantly higher body mass index, total cholesterol, homocysteine, and fibrinogen levels (Table I). However, the prevalence of CAC was similar across all hsCRP quartiles: quartiles 1-4: 55.6%, 46.8%, 44.7%, and 52.1%, respectively (P = .72). Multivariable analysis controlling for LDL cholesterol, triglycerides, body mass index, hsCRP, and the use of aspirin and statin medications found LDL cholesterol as the only variable...
that was independently associated with the presence of CAC (odds ratio 1.010, 95% confidence interval 1.001-1.020, per milligrams per deciliter of LDL).

Discussion

Postulated mechanisms for the association between hsCRP and the development of coronary heart disease include a possible relationship to the extent of coronary atherosclerosis (ie, a disease marker) or the extent of inflammation within the atherosclerosis present (ie, a process marker). In this case-control study of healthy middle-aged men, we compared hsCRP to the presence and extent of CAC, a validated atherosclerosis surrogate for the presence and extent of atherosclerosis. The principal finding of this study is the lack of a relationship between hsCRP and CAC, suggesting that the relationship between hsCRP and CHD events is the result of an active inflammatory process and not a passive marker of the presence and extent of atherosclerosis.

Several lines of evidence suggest a role for hsCRP in predicting the presence or absence of atherosclerosis. First, hsCRP is related to standard cardiac risk factors (as found in this study) and has been identified within atheroma (particularly foam cells). Second, inflammation is an essential component in the development of atherosclerosis. Studies in genetically modified mice lacking macrophage colony-stimulating factor, interleukin-8, or monocyte chemotactic protein-1 or with impaired leukocyte signaling have demonstrated the inhibition of atherosclerosis. Such data have contributed to our basic understanding of the importance of inflammation in atherogenesis. However, the relevance of different levels of “normal” inflammation on the extent of atherosclerosis development within populations of immunocompetent humans is unclear.

In contrast, the strong association of inflammatory markers with atherothrombotic coronary events in humans provides clinical evidence supporting basic data on the role of inflammation in promoting coronary plaque instability and thrombotic potential. In previous research, hsCRP has been more consistently identified within atheromatous (and potentially vulnerable) plaques compared with fibrous plaques. Furthermore, hsCRP levels are elevated in patients with clinical CAD (frequently identified by angiography) but have not been related to the extent of coronary disease on angiography or atherosclerosis measured by carotid B-mode ultrasonography. Last, our findings in middle-aged men are consistent with data from a recent study in postmenopausal women. Thus these 2 studies from very different patient populations provide strong evidence against any significant relationship between hsCRP levels and the presence and extent of calcified atherosclerosis.

Limitations

We used a validated commercial assay for the measurement of hsCRP, but variability in commercial assays may limit the external validity of these data. Our data replicate prior research on the relationship between smoking and hsCRP, thus supporting the internal validity of our hsCRP assay. We used CAC as a surrogate for coronary atherosclerotic plaque burden on
the basis of the well-established relationship between CAC and the extent of histologic plaque. However, atherosclerosis in vascular beds other than the coronary arteries could also contribute to the level of hsCRP. Last, our study population consisted of healthy middle-aged men with a relatively low prevalence of CAC. Nonetheless, males more than 35 years old almost uniformly have some atherosclerosis present. Furthermore, CAC has been validated as a marker of atherosclerosis, even in young populations. The male subjects of the PACC cohort have a CAC prevalence of 20.6%. Thus all subjects in this study are within the upper quartile of CAC extent and are believed to be at the highest risk for development of manifest CHD.

Conclusion

This study, demonstrating that hsCRP is unrelated to the presence and severity of subclinical calcified atherosclerosis, suggests that serologic inflammatory markers are principally a measure of the atheroinflammatory disease process and are not an index of the extent of coronary atherosclerotic plaque. The independent prognostic utility of quantifying calcified atherosclerosis and systemic inflammation suggests that disease and process markers of atherosclerosis may be complementary tools in coronary heart disease prediction. This hypothesis requires direct confirmation in prospective clinical trials.

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